## MAIL STOP AMENDMENT

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

H. Lowenheim

Attorney Docket No.: SOPH116953

Application No.: 09/622,719

Group Art Unit: 1635

Filed:

October 18, 2000

Examiner: K.A. Lacourciere

Title:

METHOD FOR THE TREATMENT OF DISEASES

OR DISORDERS OF THE INNER EAR

RESPONSE TO OFFICE ACTION

Seattle, Washington 98101

December 29, 2004

TO THE COMMISSIONER FOR PATENTS:

In view of the arguments that follow, and the declaration of Jonathan Kil submitted

herewith, applicant submits that all the pending claims are in condition for allowance.

Rejection of Claims 28, 31, and 63 Under 35 U.S.C. § 112, First Paragraph, for Alleged Lack of

Adequate Written Description

The Examiner argues that the genus of mammalian p27<sup>Kip1</sup> antisense required to practice

the claimed methods do not meet the written description provision of 35 U.S.C. § 112, first

paragraph, because none of the species encompassed by the genus were described in the

specification, and a sufficient number of species to represent the genus were not described in the

prior art. Additionally, the Examiner argues that the genus of mammalian p27<sup>Kip1</sup> is broad and

the species encompassed in the genus is highly variant (for example, with regard to nucleotide

sequence), and therefore the structure (i.e., nucleotide sequence) of antisense molecules targeting

this genus is highly variant.

As a preliminary matter, applicant respectfully notes that the Examiner does not provide

any basis to support the assertion that the species encompassed by the genus of mammalian

p27<sup>Kip1</sup> molecules is highly variant, for example with regard to nucleotide sequence. Applicant

submits that, on the contrary, the art teaches that the species encompassed within the genus of

mammalian nucleic acid molecules encoding p27Kip1 proteins, have highly related sequences.

For example, in the response submitted on June 9, 2004, together with the Request for Continued

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Examination, applicant provided a Clustal W Alignment of the nucleic acid sequences encoding human, mouse, and mink p27Kip1 proteins. This alignment showed that these three nucleic acid

sequences are more than 85% identical (response filed June 9, 2004, at page 7, and

Attachment D). Further, as described by Polyak et al. (Cell 78:59-66 (1994)), which was made

of record in the response dated November 4, 2003, the p27Kip1 proteins encoded by these nucleic

acid molecules are about 90% identical (Polyak et al., page 61, last line, to page 62, line 2).

Thus, applicant submits that the art teaches that the species encompassed by the genus of

mammalian p27Kip1 molecules are highly conserved.

Submitted herewith, as Attachment A, is the declaration of Jonathan Kil (hereinafter referred to as the Third Kil Declaration). A copy of Jonathan Kil's Curriculum vitae was made of record in the response dated June 9, 2004. The Third Kil Declaration describes the results of experiments in which 14 antisense oligonucleotides (directed against mouse p27Kip1 mRNA) were introduced into mouse NIH 3T3 cells, cultured in vitro, and subsequently the level of

p27Kip1 mRNA was measured.

The nucleic acid sequences of the 14 antisense oligonucleotides are set forth in Table 1, paragraph 3, of the Third Kil Declaration. As described in paragraph 3 of the Third Kil Declaration, the location of each oligonucleotide is given with reference to the sequence of the mouse p27<sup>Kip1</sup> cDNA (GenBank accession number U09968; reported in Polyak, K., et al.

Cell 78: 56-66 (1994).

As described in paragraph 3 of the Third Kil Declaration, the cells were incubated in the presence of the oligonucleotide for 26 hours. Real time PCR was used to measure the amount of p27<sup>Kip1</sup> mRNA present in total RNA extracted from the treated cells.

Enclosed herewith as Attachment B is a graph showing the level of p27<sup>Kip1</sup> mRNA in the cells treated with the different oligonucleotides, compared to the control level of p27Kip1 mRNA in cells treated with the Lipofectamine lipid delivery vehicle without oligonucleotides. As described in paragraph 4 of the Third Kil Declaration, the results shown in the graph demonstrate

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that all of the tested oligonucleotides caused a significant reduction in the level of p27<sup>Kip1</sup>

mRNA in the treated cells.

As can be seen from Table 1 of the Third Kil Declaration, the antisense oligonucluotides

each corresponded to a different sequence within the first 445 bases of the p27Kip1 mRNA.

Thus, the results of these experiments are consistent with the view that the level of expression of

a p27Kip1 mRNA can be significantly reduced by an antisense oligonucleotide that corresponds

to any sequence of at least 14 consecutive nucleotides within a p27<sup>Kip1</sup> mRNA. Consequently,

in this case the applicant submits that the written description requirement is satisfied by the

existence, in the prior art, of the nucleic acid sequence of at least one member of the highly

conserved genus of mammalian p27Kip1 mRNAs (e.g., the sequence of the mouse p27Kip1

cDNA, set forth in the GenBank database as accession number U09968, which was reported by

Polyak et al. in 1994) that can be used as a source of antisense oligonucleotide sequences.

Consequently, applicant requests withdrawal of the rejection of Claims 28, 31, and 63

under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing arguments, and the results of the experiments described in the Third Kil Declaration, applicant respectfully submits that all the pending claims are in condition

for allowance. Reconsideration and favorable action are requested.

Respectfully submitted,

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